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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,395	04/27/2007	Ronald W. Wood	176/61672(1246)	1398

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EXAMINER	
QIAN, CELINE X	
ART UNIT	PAPER NUMBER
1636	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,395	WOOD ET AL.	
	Examiner	Art Unit	
	CELINE X. QIAN	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/3/2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/7/06* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0810*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17 are pending in the application.

This Office Action is in response to the Amendment filed on 8/3/2010.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 8/3/2010 has been considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection has been re-written to address the amendment.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to

make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention:

The claimed invention is drawn to a method of diagnosing a pelvic pain disorder comprising measuring a level of CGRP in the patient sample in relation to a standard level in a normal asymptomatic population, wherein the measured level of CGRP is elevated indicates the diagnosis of a pelvic pain disorder. The claimed invention is also drawn to a method of determining predisposition of an individual to conditions associated with pelvic pain disorder comprising measuring a level of CGRP in the patient sample in relation to a standard level in a normal asymptomatic population, wherein the measured level of CGRP or PACAP, or both is elevated indicates the individual is predisposed to conditions associated with a pelvic pain disorder.

The breadth of the claim:

The breadth of the claim is very broad. The independent claims are drawn to a method of either diagnosing or predicting any type of pelvic pain disorder based on the level of CGRP present in any tissue or body fluids. The pelvic pain disorder encompasses any disorder of known or unknown cause which has the symptom of pelvic pain, including interstitial cystitis, Crohn's disease, ulcerative colitis, irritable bowel syndrome…etc. As such, the breadth of the claimed method is very broad.

The teaching of the specification and the presence of working examples:

The specification discloses a method of diagnosing a pelvic pain disorder comprising measuring a level of CGRP in the patient sample in relation to a standard level in a normal

asymptomatic population, wherein the measured level of CGRP is elevated indicates the diagnosis of a pelvic pain disorder. The specification also discloses a method of determining predisposition of an individual to conditions associated with pelvic pain disorder comprising measuring a level of CGRP in the patient sample in relation to a standard level in a normal asymptomatic population, wherein the measured level of CGRP is elevated indicates the individual is predisposed to conditions associated with a pelvic pain disorder. However, aside from the prophetically teaching that CGRP may be used to predicting the predisposition and diagnosing pelvic pain associated disorder, the specification fails provide any evidence that such method would actually work in human or in any animal model of such disease. In Example 1 and 2, the specification discloses that 15 patient suffer from one type of pelvic pain associated disorder, interstitial cystitis (IC), has elevated CGRP peptide in their urine compared to the 9 control individual who do not have this disease. The specification discloses that 75% of IC patients have CGRP levels greater than 1.92 ng/mg creatinine, and that 75% of control subjects have level less than 1.82 ng/mg creatinine. However, whether diagnosing or determining predisposition of any disorder associated with pelvic pain based on CGRP is unpredictable because the small sample size and small difference between patient and standard control of a single experiment does not establish how the determination of pelvic pain disorder may be diagnosed or predicted. According to the data in Figure 2, the range of the level of CGRP of patients overlaps with the range of the control even without considering the standard deviation. In other words, if the level of CGRP present in a urine sample is 1.90 ng/mg creatinine, does this person have pelvic pain disorder? Furthermore, the specification does not disclose whether the elevated level of CGRP is resulted from IC or preceded from the development of IC. As such, it

is unclear how to determine the predisposition of IC based on such finding. The specification also fails to disclose whether other types of pelvic pain disorder, for example, Crohn's disease, ulcerative colitis, which different mechanism from IC, also has elevated CGRP in urine. As such, whether any type of pelvic pain disorder may be diagnosed or predicted based on CGRP is unpredictable.

The state of prior art and the level of prediction in the prior art:

The state of prior art at the time of filing is silent on whether measuring the level of CGRP may be used to determine the predisposition and diagnosing any pelvic pain disorder. Kreder et al. (IDS) disclose that CGRP level is elevated in the urine sample of IC patients following chlorpactin treatment. Kreder et al. disclose that IC patients has very low level of CGRP in urine sample pre and post-hydrodistention, the level only elevated following chlorpactin treatment. Kreder et al. speculate that chlorpactin works by increased releasing of CGRP from nociceptive nerve terminals. In view of this teaching, it appears that CGRP level in urine is not related to the IC itself, rather, the treatment of cholorpactin may be responsible for such elevation. As such, whether the level of CGRP may be used to predict a predisposition or diagnose pelvic disorder is unpredictable.

In summary, neither the specification nor the prior art establishes a nexus between elevated level of CGRP in any type of tissue and pelvic disorder diagnosis or disposition. In view of lack of teaching from the specification and prior art, the skilled artisan would have to engage in undue experimentation to practice the method as claimed. Therefore, the claimed invention is not enabled by the instant specification.

Response to Arguments

In response to this rejection, Applicants argue that it is well established that crosstalk exists between different pelvic organs, whereby stimulation of non-bladder afferent produces measurable affects on the bladder as evidenced by Pezzone et al. Applicants assert that irritable bowel syndrome, interstitial cystitis, and other chronic pelvic pain disorders often occur concomitantly, and provide compelling evidence that afferent irritation of one pelvic organ can adversely influence and sensitize another pelvic organ via neuronal interaction. Applicants further cite Ustinova et al. to demonstrate that mast cell infiltration as well as urinary bladder C fibers and the release of their active neuropeptides in the pelvic cross-sensitization process. Applicants further cite Sarna to demonstrate that close intra-arterial infusion of CGRP to the proximal intestinal segment can produce changes in heart rate just like bowel distension, whereas Delafoy et al. confirms CGRP is implicated in several visceral pain. Applicants also assert that the teaching of Bourdu et al. confirms that CGRP receptor antagonist inhibits colonic pain hypersensitivity and suggests CGRP receptor provide a promising target for treatment of IBS. Applicants conclude that CGRP can be used as a measure of pelvic pain syndromes generally because the substantial cross talk between pelvic organs and the association of CGRP in visceral pain involving these organs. Applicants also argue that the example in the application demonstrate a statistically significant relationship between bladder CGRP levels and interstitial cystitis, which is confirmed by Mann Whitney non-parametric test and the one way analysis of variance was also significant. Applicants assert that since interstitial cystitis has been previously diagnosed, the skilled artisan would recognize that the combination of elevated CGRP plus the symptoms can be used to diagnose interstitial cystitis. Lastly, Applicants assert that although

prior art teaches away from the claimed invention, it does not negate the enablement of the claimed invention.

The above argument has been fully considered but deemed unpersuasive. The detailed reason for non-enablement of the claimed invention has been discussed in the previous office action and above. Applicants are reminded the rejection is not based on any single factor but a thorough analysis of all wands factors, including (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art. The prior art cited by Applicants does not support the enablement of the claimed invention, that is, predicting the likelihood of a person will develop pelvic pain disorder or diagnose such disorder based on the level of CGRP from any tissue. The disclosure of Pezzone et al. and Ustinova et al. fail to even mention the involvement of CGRP in any of the pelvic pain disorder. While Sarna discloses intra-arterial infusion of CGRP to proximal intestinal segment can produce increased heart rate as observed with giant migrating contraction, Delafoy et al. discloses that CGRP is implicated in several models of visceral pain, and Bourdu et al. discloses CGRP receptor antagonist inhibits colonic pain hypersensitivity, none of the reference teach a correlation between increased expression of CGRP endogenously and the likelihood of a patient develop pelvic pain disorder or being diagnosed with pelvic pain disorder. The involvement of CGRP for signal transduction in pain, such as migraine, is well known. However, there is no report teach there is correlation between increased expression of CGRP and prognosis or diagnosis for pelvic pain. Receptor

hypersensitivity does not necessarily mean that the ligand is over-expressed, it may be the result of sensitization of the receptor or constitutive activation of the receptor. As such, the cited prior art does not support the enablement of the claimed invention. With regard to Applicants' argument directed to statistical significance, Applicants are reminded that the specification fails to provide a method to determine what level of CGRP is indicative of predisposition of pelvic disorder, or to diagnosis of pelvic disorder. As discussed in the rejection, according to the data in Figure 2, the range of the level of CGRP of patients overlaps with the range of the control even without considering the standard deviation. In other words, if the level of CGRP present in a urine sample is 1.90 ng/mg creatinine, does this person have pelvic pain disorder? Furthermore, the specification does not disclose whether the elevated level of CGRP is resulted from IC or preceded from the development of IC. As such, it is unclear how to determine the predisposition of IC based on such finding. Lastly, Applicants indicate that the data is based on patients already be diagnosed with interstitial cystitis. In fact, without prior knowledge of whether a patient has interstitial cystitis, whether a skilled in the art can predict if the patient will develop said disease or other type of pelvic disorder is unpredictable because it is unclear what value is considered high based on one single experiment. Moreover, even if the patient already exhibit a symptom, for example, abdominal pain, whether a skilled artisan can diagnose a pelvic pain disorder either being crohn's disease, interstitial cystitis, or colonic disorder is unpredictable because CGRP is involved in generally all types of pelvic pain as alleged by the specification. Therefore, for reasons set forth in the previous office action and above, this rejection is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE X. QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian /
Primary Examiner, Art Unit 1636